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EXAMINER	
PATEL, SUDHAKER B	
ART UNIT	PAPER NUMBER
1624	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/002,326	Applicant(s) Stefan Peukert et al
	Examiner SUDHAKER PATEL,D.Sc.Tech.	Art Unit 1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 1, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above, claim(s) *4* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3 and 5-18* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *1,5*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

I. *Election/Restriction*

1. Applicant's election with traverse of species of Example 23 as recited on page 45 of the specification in Paper No. 7 dated 4/1/03 is acknowledged. The traversal is on the ground(s) that the examination of the application as a single piece will not be a serious burden to the Examiner. This is not found persuasive because the rings and radicals within the definition of A1-A4 and A5-A8 together with R1-R4 and R30,R31 are diverse in scope. A prior art reference, which anticipates one member of either A1-A4 or A5-A8 such as pyridyl(when one of A1-A8 is N) or diazines(when 2 of A1-A8 are N), under 35 U.S.C. 102, would not render obvious another member such as phenyl(under 35 U.S.C. 103.

Additionally, A1-A8 independently of one another can be N, CH or CR5, with the proviso that at least one of these groups being N and at least 4 of these groups being CH, and R14, R16 can further provide N-containing heteroaromatic ring(s) having 1-9 carbon atoms. This will involve different classes as per U.S. Patent classification system. e.g. following "Hits" for searches are involved.

Class 546(i.e 6-membered ring): 2249.

Class 540(i.e. 7-membered ring): .

Class 544(i.e. 6-membered ring with 1,2 diazine, 1,3-diazine, 1,4-diazine):4711.

Therefore, search for above hits together with various utility class 514 (= 8001 hits) is a burden for a through examination of this application as a single piece .

Applicants elected species consisting of following variables:

A4 =N;

A1-A3 =CH;

A5-A8 =CH;

R1 =-COOR9;

R2 =H;

R30/R31 =H;

R4 =H;

R3 -CH2-R16 .

Applicants are reminded of the election of species guidelines provided in MPEP 803.02, which are followed for examination.

The elected species was not found in the prior art. When the search was expanded to species with:

Any **one** of A1-A4 =N;

A5-A8 =**CH or 1 of A5-A8** = N;

R1 =-COOR9;

R2 =H;

-C(R30)(R31) =CO;

R4 =H;

R3 =-CH2-R16 = -CH2-Alkyl,

art was found.

Thus, the bridge -C(R30)(R31)-N(R2)R1) is: = -CO-NH-CO-O-alkyl, and the bridge -CO-N(R4)(R3) is: = -CONH-AlkylC2-6.

As per the guide lines stated above, the examination was limited to compounds of Formula(I) of generic claim 1 as stated above.

All other definitions of R1 (= SO2R(10), COR11,CONR12R13,CSNR12R13), R14 (= CF3,C2F5,C3F7,CH2F,CHF2,OR15,SO2Me, furyl, thienyl, N-containing heteroaromatic rings with 1-9 carbon atoms), R16(=CF3,C2F5,C3F7,CH2F,CHF2,OR17,SO2Me, furyl, thienyl, N-containing heteroaromatic rings with 1-9 carbon atoms), the diazine ring combinations(diazine-phenyl or phenyl-diazine or diazine:diazine), claim 4 are withdrawn from consideration as being directed to non-elected invention. See 37 CFR 1.141(a) and MPEP 821.02. Since, claims 1-3,5-18 link with other inventions, this application will be examined bearing in mind the subject matter and species as elected by the applicants only.

The requirement is still deemed proper and is therefore made FINAL.

First action on merits follows.

II. ***Information Disclosure Statement***

Information Disclosure statement submitted as papers #1 ½, # 5 dated 12/05/01 and 5/10/02 are considered by the examiner and signed copies of PTO Forms 1449 are enclosed with this communication for applicants' record.

III. Claim 1 is Markush type claim which is generic to elected invention. The claim lack unity of invention for the reasons outlined above. Accordingly, the Markush type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability. See MPEP 803.02.

Claims 1-3,5-18 are rejected on the grounds that the claims are drawn to improper Markush group. In re Harnisch, 206 USPQ 300, state that a unity of invention exists where compounds included within a Markush Group (1) share are a common utility and (2) share a substantial structural feature disclosed as being essential to that utility. In the instant case, the claimed subject matter does not share a substantial structural feature disclosed as being essential to that utility.

The requirement for a proper Markush claim is that it includes only substances that in their physical, chemical and physiological characteristics are functionally equivalent. The members of the instant Markush Groups possess widely different, physical and chemical properties. The compounds are not considered functionally equivalent and are so diverse that they demonstrate dissimilar and unrelated properties. The mere fact that there is structural similarity in pharmaceutical agents is not in itself reason to render all the embodiments functionally equivalent.

The improper Markush groups are variables A1-A8 wherein either one of A1-A8 is N and the rest are CH, CR5 or 2 of A1-A8 are N and the rest are CH, CR5 R3 and may form combinations: 1). Pyridine-Phenyl or

2). Pyridine-Pyridine;

3). 1,2-diazine-Phenyl or

4). 1,3 diazine-Phenyl or

5). 1,4-diazine-Phenyl or

6). 1,2-diazine-Pyridine or

7). 1,4-diazine-Pyridinel or

8). 1,4-diazine-Pyridine or

9). Various combinations of diazine-diazine rings and other possibilities as per claim 1 and the substituents R1-R4, R30,R31, R5 which may be further substituted by one or more substituents.

Amending the claim to elected invention would overcome the improper Markush rejection.

IV. *Claim Rejections - 35 U.S.C. § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3,5-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards

as the invention. Following reasons apply. Any claim not specifically rejected is rejected as being dependent on a rejected claim.

(A). Claim 1 recites for variables R14,R16: " substituted by 1, 2, or 3 substituents chosen from. many groups". It is not very clear as to what applicants want to claim. These groups can occupy any carbon atom e.g. N-containing heterocycle having 1-9 carbon atoms. Chemically, there is no heterocycle with 1 carbon and 1 N. It can be minimum with 2 C and 1 N. 2. Correction is required.

(B). Claims 1, 2,3, 5,6,7,8 recite: " a compound of Formula (I) or a pharmaceutically tolerable salt thereof, in an stereoisomeric form, or a mixture of any such compounds in any ratio" . It is not very clear as to isomeric form or a mixture of any such compound". Correction is required as: " a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or an stereoisomeric form thereof, or a racemic mixture thereof." .

(C). Claims 9 recites " a pharmaceutical preparation comprising an efficacious amount of at least one of the compounds of claim 1 and at least one additional component from pharmaceutically acceptable vehicles, pharmaceutically acceptable additives and other pharmacological active compounds".".It is not very clear as to what applicants want to claim by stating:" other pharmacological active compound". The process of preparation and the exact make of the same is not told to us.. Correction to " a pharmaceutical composition comprising therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt ,

or an stereoisomeric form , or a racemic mixture thereof, and a pharmaceutically acceptable carrier" is required.

(D). Claims 16-18 recite complex pharmaceutical preparations consisting(where applicable) of :

Efficacious amount of at least one compound of claim 1;

At least one Ikr channel blocker;

At least one Iks channel blocker;

At least one beta blocker.

The claims do not exactly define: (a). The process or step of preparing the pharmaceutical preparation, (b). The Ikr, Iks,and beta blocker are not definite, (c). At least one term does not say exactly what is required because it leaves open end for the other possibilities,(d). Pharmaceutically acceptable vehicles and additives are also do not describe the exact make up of the pharmaceutical preparation. Correction(s) are required.

V. Claims 10-14 recite " a method for treating or preventing K+ channel-mediated diseases, cardiac arrhythmias, reentry arrhythmias, supraventricular arrhythmias, atrial fibrillation or atrial flutters", and claim 15 recites" a method for terminating atrial fibrillation or atrial flutters" respectively. These terms include diseases which are yet to be discovered.

Claims 9-18 will also raise the issue of enablement under 35 U.S.C. 112.

MPEP 806.05(h) provides for restriction of method of use claims, where they show more than one use of the compounds.

The statement related to utility in claims 10-15 cannot be acceptable as one specific utility. The recent utility guidelines set up by USPTO require applicants to meet the requirements as stated in Brenner v. Manson in 148 USPQ 689, which requires that utility be developed to a point where "specific benefits exists in currently available form" similar is
the "immediate benefit to the public: standard set forth in the concurring opinion of In re Hartop, 135 USPQ 419 is whether the invention has been brought to such perfection as to be capable of practical employment. This language is echoed in Bindra vs. Kelly, 206 USPQ 570.

The " how to use" requirements of 35 U.S.C. 112 are not met by disclosing only a pharmacological activity of the claimed compounds if one skilled in the art would not be able to use the compounds effectively without undue experimentation. In re Driedrich (CCPA 1963) 318 F.2d 946, 138 USPQ 128; In re Garner et al. (CCPA 1970) 427 F2d 786, 166 USPQ 138. Thus, the compounds as claimed in claim 1 are not structurally similar to known compounds having the same activity, and their pharmaceutical properties could not be predicted based on their structure/chemical molecule, a disclosure that they possess a particular activity against a biological property described as: "a method for treating or preventing K+ channel-mediated diseases, cardiac arrhythmias, reentry arrhythmias, supraventricular arrhythmias, atrial fibrillation or atrial flutters", and a method for terminating atrial fibrillation or atrial flutters ". The same may not suffice as a description of how to use as required by 35 U.S.C. 112. In re Moureu et al (CCPA 1965)345 F2d 595, 145 USPQ 452. activity. Correction is required.

VI. ***Claim Rejections - 35 U.S.C. § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3,5-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamber et al(U.S.P. 4616002).

Applicants' compounds have a core: orthosubstituted phenyl/pyridin-orthosubstituted pyridine", and its utility as method of treating K+-channel-mediated diseases.

Kamber teaches dihydro pyridine compounds, compositions and utility for treating cardiovascular disorders. See compounds of Formula(I) of abstract, and compounds of claims 1-2 in columns 55-58 wherein Ar = monocyclic aryl or a six membered monocyclic heteroaryl which are phenyl and pyridyl which are substituted by Ac, R2, R3 (in pyridine core), and aryl/pryridine core having alkyl, alkoxy, OH, COOH or, alkoxycarbonyl, carbamoyl, N-loweralkylcarbamoyl.

The instantly claimed compounds differ from Kamber by having the bridge -CO-N(R2)R1) = -CO-NH-CO-O-alkyl. The ref. '002 does teach making of compounds with bridges: -CO-NH-**CH2**-CO-OR7 and -CO-N(R4)(R3) = -CONH-Alkyl = N-loweralkylcarbamoyl.

One skilled in this art would find ample motivation from prior art(s) to try out existing core of either pyridine-pyridine or phenyl-pyridine, and modify the -COOH or -NH2 or -CN groups to -CO-NH-CO-O-alkyl or -CO-N(R4)(R3) by using conventional chemistry of making

amides/amines/acids, substituted amides, and intermediates e.g.-CH2OH, -CH2-halogen from -COOH group, and the expectation that compounds so structurally similar would be expected to possess pharmaceutical properties as claimed herein.(in re Wood, 199 USPQ 137).

Claims 1-3,5-15 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Urbans et al(U.S.P. 5670525).

Urban teaches making of substituted 4-phenyl-6-amino-nicotinic acid compounds of Formula(I), and also teaches their utility for treating diseases which are affected by modulating the Calcium-dependent potassium channel. See abstract and claim 1 in columns 15-16 wherein A = aryl or pyridine which can be substituted by NO2, CN, halogen, CF3, alkoxy, D = CN or NO2, R2/R3 = acyl, alkyl or H, R1 = H, or alkyl.

The reference differs from the instant compounds by not having the specific bridge: -CO-N(R2)R1) = -CO-NH-CO-O-alkyl. However, the ref. '524 does teach making of compounds with bridges: --NH--CO-alkyl and the bridge -NH-Alkyl., and other substituents e.g. D = CN or NO2; alkyl/methyl, R1 = alkyl or H; R2/R3 = alkyl, acyl, .

However, one skilled in pharmaceutical art would find ample motivation from prior art(s) to try out either phenyl-pyridine or pyridine-pyridine core(s) of the compounds for the modifications by trying out various positions and their combinations for the substituents as recited herein, and the expectation that compounds so structurally similar would be expected to possess pharmaceutical properties as claimed herein.(in re Wood, 199 USPQ 137).

It has been held that a prior art disclosed compounds is sufficient to render a prima facie case of obviousness as species falling within a genus. See In re SUSI, 440 F 2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by Federal Circuit in Merck & co. V. Biocraft Laboratories, 847 F 2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir.1989).See In re Dillon 16 USPQ 2nd. 1897, 1923 regarding a prima facie case of obvious ness of structurally similar compounds disclosed by prior art(s) regardless of the properties disclosed in the inventor's application.

All this is especially considered so in the absence of timely, verified, comparative data, commensurate in scope to the claims sought, clearly and convincingly proving obvious ness over the art(s) as applied above. If applicants intend to rely on unusual or unforseen results demonstrate patentability, attention is drawn to MPEP 716. It is also pointed out that arguments of patentability to differences either not in, or not made clear by, claim language will be of no avail as it is the claims, per se, that are the measure of the invention.

VII. *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker Patel, D.Sc. Tech., whose telephone number is (703) 308 4709.

The examiner can normally be reached on Monday thru' Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by the phone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah can be reached at (703) 308 4716 or Sr. Examiner Mr. Richard Raymond at (703)308 4523.

A facsimile center has been established for Group 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4556 or (703) 305-3592.

Any inquiry of general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 1235.

Mukund Shah

sp

Supervisory Patent Examiner

April 16, 2003

Art Unit 1624